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(71) Applicant *(for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BF, BG, BJ, BR, BW, BY, BZ, CA, CF, CG, CH, CI, CM, CN, CO, CR, CU, CY, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, FR, GA, GB, GD, GE, GH, GM, GN, GQ, GR, GW, HR, HU, ID, IE, IL, IN, IS, IT, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MC, MD, MK, ML, MN, MR, MW, MX, MZ, NA, NE, NG, NI, NL, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG only)*: **ASTRAZENECA AB** [SE/SE]; S-SE-151 85 Södertälje (SE).

(71) Applicant *(for MG only)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London Greater London W1K 1LN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **JOHNSTONE, Craig** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **MCKERRECHER, Darren** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **PIKE, Kurt, Gordon** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **WARING, Michael, James** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, SE-151 85 Södertälje (SE).

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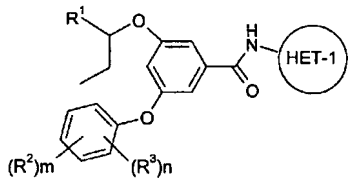
(54) Title: PHENOXY BENZAMIDE COMPOUNDS WITH UTILITY IN THE TREATMENT OF TYPE 2 DIABETES AND OBESITY



(I)

(57) Abstract: Compounds of Formula: (I); wherein: R^1 is methoxymethyl; R^2 is selected from $-C(O)NR^4R^5$, $SO_2NR^4R^5$, $S(O)_pR^4$ and HET-2; HET-1 is a 5- or 6-membered, optionally substituted C-linked heteroaryl ring; HET-2 is a 4-, 5- or 6-membered, C- or N-linked optionally substituted heterocyclyl ring; R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano; R^4 is selected from for example hydrogen, optionally substituted (1-4C)alkyl and HET-2; R^5 is hydrogen or (1-4C)alkyl; or R^4 and R^5 together with the nitrogen atom to which they are attached may form a heterocyclyl ring system as defined by HET-3; HET-3 is for example an optionally substituted N-linked, 4, 5 or 6 membered, saturated or partially unsaturated heterocyclyl ring; p is (independently at each occurrence) 0, 1 or 2; m is 0 or 1; n is 0, 1 or 2; provided that when m is 0, then n is 1 or 2; or a salt, pro drug or solvate thereof, are described. Their use as GLK activators, pharmaceutical compositions containing them, and processes for their preparation are also described.

WO 2006/040528 A1

PHENOXY BENZAMIDE COMPOUNDS WITH UTILITY IN THE TREATMENT OF TYPE 2 DIABETES AND OBESITY

The present invention relates to a group of benzoyl amino heterocyclyl compounds which are useful in the treatment or prevention of a disease or medical condition mediated through glucokinase (GLK or GK), leading to a decreased glucose threshold for insulin secretion. In addition the compounds are predicted to lower blood glucose by increasing hepatic glucose uptake. Such compounds may have utility in the treatment of Type 2 diabetes and obesity. The invention also relates to pharmaceutical compositions comprising said compounds and to methods of treatment of diseases mediated by GLK using said compounds.

In the pancreatic β-cell and liver parenchymal cells the main plasma membrane glucose transporter is GLUT2. Under physiological glucose concentrations the rate at which GLUT2 transports glucose across the membrane is not rate limiting to the overall rate of glucose uptake in these cells. The rate of glucose uptake is limited by the rate of phosphorylation of glucose to glucose-6-phosphate (G-6-P) which is catalysed by glucokinase (GLK) [1]. GLK has a high (6-10mM) Km for glucose and is not inhibited by physiological concentrations of G-6-P [1]. GLK expression is limited to a few tissues and cell types, most notably pancreatic β-cells and liver cells (hepatocytes) [1]. In these cells GLK activity is rate limiting for glucose utilisation and therefore regulates the extent of glucose induced insulin secretion and hepatic glycogen synthesis. These processes are critical in the maintenance of whole body glucose homeostasis and both are dysfunctional in diabetes [2].

In one sub-type of diabetes, Maturity-Onset Diabetes of the Young Type 2 (MODY-2), the diabetes is caused by GLK loss of function mutations [3, 4]. Hyperglycaemia in MODY-2 patients results from defective glucose utilisation in both the pancreas and liver [5]. Defective glucose utilisation in the pancreas of MODY-2 patients results in a raised threshold for glucose stimulated insulin secretion. Conversely, rare activating mutations of GLK reduce this threshold resulting in familial hyperinsulinism [6, 6a, 7]. In addition to the reduced GLK activity observed in MODY-2 diabetics, hepatic glucokinase activity is also decreased in type 2 diabetics [8]. Importantly, global or liver selective overexpression of GLK prevents or reverses the development of the diabetic phenotype in both dietary and genetic models of the disease [9-12]. Moreover, acute

treatment of type 2 diabetics with fructose improves glucose tolerance through stimulation of hepatic glucose utilisation [13]. This effect is believed to be mediated through a fructose induced increase in cytosolic GLK activity in the hepatocyte by the mechanism described below [13].

Hepatic GLK activity is inhibited through association with GLK regulatory protein (GLKRP). The GLK/GLKRP complex is stabilised by fructose-6-phosphate (F6P) binding to the GLKRP and destabilised by displacement of this sugar phosphate by fructose-1-phosphate (F1P). F1P is generated by fructokinase mediated phosphorylation of dietary fructose. Consequently, GLK/GLKRP complex integrity and hepatic GLK activity is regulated in a nutritionally dependent manner as F6P is dominant in the post-absorptive state whereas F1P predominates in the post-prandial state. In contrast to the hepatocyte, the pancreatic β-cell expresses GLK in the absence of GLKRP. Therefore, β-cell GLK activity is regulated extensively by the availability of its substrate, glucose. Small molecules may activate GLK either directly or through destabilising the GLK/GLKRP complex. The former class of compounds are predicted to stimulate glucose utilisation in both the liver and the pancreas whereas the latter are predicted to act selectively in the liver. However, compounds with either profile are predicted to be of therapeutic benefit in treating Type 2 diabetes as this disease is characterised by defective glucose utilisation in both tissues.

GLK, GLKRP and the K_{ATP} channel are expressed in neurones of the hypothalamus, a region of the brain that is important in the regulation of energy balance and the control of food intake [14-18]. These neurones have been shown to express orectic and anorectic neuropeptides [15, 19, 20] and have been assumed to be the glucose-sensing neurones within the hypothalamus that are either inhibited or excited by changes in ambient glucose concentrations [17, 19, 21, 22]. The ability of these neurones to sense changes in glucose levels is defective in a variety of genetic and experimentally induced models of obesity [23-28]. Intracerebroventricular (icv) infusion of glucose analogues, that are competitive inhibitors of glucokinase, stimulate food intake in lean rats [29, 30]. In contrast, icv infusion of glucose suppresses feeding [31]. Thus, small molecule activators of GLK may decrease food intake and weight gain through central effects on GLK. Therefore, GLK activators may be of therapeutic use in treating eating disorders, including obesity, in addition to diabetes. The hypothalamic effects will be additive or

synergistic to the effects of the same compounds acting in the liver and/or pancreas in normalising glucose homeostasis, for the treatment of Type 2 diabetes. Thus the GLK/GLKRP system can be described as a potential "Diabesity" target (of benefit in both Diabetes and Obesity).

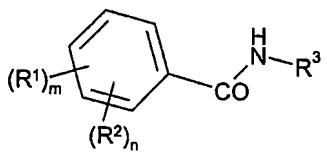
GLK is also expressed in specific entero-endocrine cells where it is believed to control the glucose sensitive secretion of the incretin peptides GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (Glucagon-Like Peptide-1) from gut K-cells and L-cells respectively (32, 33, 34). Therefore, small molecule activators of GLK may have additional beneficial effects on insulin secretion, b-cell function and survival and body weight as a consequence of stimulating GIP and GLP-1 secretion from these entero-endocrine cells.

In WO00/58293 and WO01/44216 (Roche), a series of benzylcarbamoyl compounds are described as glucokinase activators. The mechanism by which such compounds activate GLK is assessed by measuring the direct effect of such compounds in an assay in which GLK activity is linked to NADH production, which in turn is measured optically - see details of the *in vitro* assay described hereinafter. Compounds of the present invention may activate GLK directly or may activate GLK by inhibiting the interaction of GLKRP with GLK.

Further GLK activators have been described in WO03/095438 (substituted phenylacetamides, Roche), WO03/055482 (carboxamide and sulphonamide derivatives, Novo Nordisk), WO2004/002481 (arylcarbonyl derivatives, Novo Nordisk), and in WO03/080585 (amino-substituted benzoylaminoheterocycles, Banyu).

Our International application Number: WO03/000267 describes a group of benzoyl amino pyridyl carboxylic acids which are activators of the enzyme glucokinase (GLK).

Our International application Number: WO03/015774 describes compounds of the Formula (A):



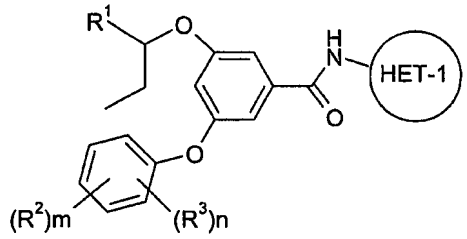
(A)

wherein R^3 is a substituted heterocycle other than a carboxylic acid substituted pyridyl.

International application WO2004/076420 (Banyu) describes compounds which are generally a subset of those described in WO03/015774, wherein for example R^1 is an (substituted) alkyl ether and R^2 is (substituted) phenoxy.

We have surprisingly found a small group of compounds, generally a selected subgroup of those described in WO 03/015774, which have generally superior potency for the GLK enzyme, and more advantageous physical properties, including, for example, higher aqueous solubility, higher permeability, and/or lower plasma protein binding. Consequently, such compounds having a balance of these properties would be expected to display higher plasma free drug levels and superior in vivo efficacy after oral dosing as determined, for example, by activity in Oral Glucose Tolerance Tests (OGTTs). Therefore this group of compounds would be expected to provide superior oral exposure at a lower dose and thereby be particularly suitable for use in the treatment or prevention of a disease or medical condition mediated through GLK.

Thus, according to the first aspect of the invention there is provided a compound of Formula (I):



(I)

wherein:

R^1 is methoxymethyl;

R^2 is selected from $-C(O)NR^4R^5$, $-SO_2NR^4R^5$, $-S(O)_pR^4$ and HET-2;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 4-, 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring

may optionally be oxidised to a S(O) or $S(O)_2$ group, which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano;

R^4 is selected from hydrogen, (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$], (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and HET-2;

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4;

R^7 is selected from $-OR^5$, (1-4C)alkyl, $-C(O)$(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an N-linked, 7 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further heteroatom (in addition to the linking N atom) independently selected from O, S and N, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- group and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an 6-10 membered bicyclic saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further nitrogen atom (in addition to the linking N atom), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-; which ring is optionally substituted on

an available carbon or nitrogen atom by 1 substituent selected from hydroxy (not on nitrogen) and R^3;

R^8 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkylamino, di(1-4C)alkylamino, HET-3 (wherein said ring is unsubstituted), (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-4 is a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S;

p is (independently at each occurrence) 0, 1 or 2;

m is 0 or 1;

n is 0, 1 or 2;

provided that when m is 0, then n is 1 or 2;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention there is provided a compound of formula (I), or a salt, pro-drug or solvate thereof as hereinbefore defined, with the proviso that compounds exemplified in WO2004/076420, which would otherwise fall within the scope of this invention, are excluded. In particular, Example numbers 9, 17, 18, 20, 129 and 135 of WO2004/076420 are excluded.

In another aspect of the invention, there is provided a compound of the formula (I) as hereinbefore defined, wherein

R^1 is methoxymethyl;

R^2 is selected from $-C(O)$-HET-3 and $-SO_2$-HET-3;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 4-, 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring may optionally be oxidised to a S(O) or $S(O)_2$ group, which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano;

R^4 is selected from hydrogen, (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$], (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and HET-2;

R^5 is hydrogen or (1-4C)alkyl; or

R^4 and R^5 together with the nitrogen atom to which they are attached may form a heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4;

R^7 is selected from $-OR^5$, (1-4C)alkyl, $-C(O)$(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-3 is an N-linked, 4, 5 or 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an N-linked, 7 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further heteroatom (in addition to the linking N atom) independently selected from O, S and N, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- group and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an 6-10 membered bicyclic saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further nitrogen atom (in addition to the linking N atom) wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-; which ring is optionally substituted on an available carbon or nitrogen atom by 1 substituent selected from hydroxy (not on nitrogen) and R^3;

R^8 is selected from $-OR^5$, (1-4C)alkyl, $-C(O)$(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkylamino, di(1-4C)alkylamino, HET-3 (wherein said ring is unsubstituted), (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-4 is a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S;

p is (independently at each occurrence) 0, 1 or 2;

m is 0 or 1;

n is 0, 1 or 2;

provided that when m is 0, then n is 1 or 2;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention there is provided a compound of the formula (I), as hereinbefore defined or a salt, pro-drug or solvate thereof, wherein:

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8.

In another aspect of the invention, there is provided a compounds of the formula (I) as hereinbefore defined, wherein

R^1 is methoxymethyl;

R^2 is selected from $-C(O)NR^{41}R^{51}$, $-SO_2NR^{41}R^{51}$ and $-S(O)_pR^{41}$;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 4-, 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring may optionally be oxidised to a S(O) or $S(O)_2$ group, which ring is optionally substituted

on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano;

R^{41} is selected from (1-4C)alkyl [substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$], (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and HET-2;

R^{51} is hydrogen or (1-4C)alkyl;

R^4 is selected from (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$], (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and HET-2;

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4;

R^7 is selected from $-OR^5$, (1-4C)alkyl, $-C(O)$(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-3 is an N-linked, 4, 5 or 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an N-linked, 7 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further heteroatom (in addition to the linking N atom) independently selected from O, S and N, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- group and wherein a sulphur atom in the ring may optionally be oxidised to a

S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an 6-10 membered bicyclic saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further nitrogen atom (in addition to the linking N atom) wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-; which ring is optionally substituted on an available carbon or nitrogen atom by 1 substituent selected from hydroxy (not on nitrogen) and R^3;

R^8 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkylamino, di(1-4C)alkylamino, HET-3 (wherein said ring is unsubstituted), (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-4 is a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S;

p is (independently at each occurrence) 0, 1 or 2;

m is 0 or 1;

n is 0, 1 or 2;

provided that when m is 0, then n is 1 or 2;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention there is provided a compound of the formula (I) as hereinbefore defined, or a salt, pro-drug or solvate thereof, wherein:

R^4 is selected from hydrogen, (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$], and HET-2;

HET-3 as an 6-10 membered bicyclic saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further nitrogen atom (in addition to the linking N atom) wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, is optionally substituted on an available carbon or nitrogen atom by 1 substituent selected from R^3.

In another aspect of the invention, there is provided a compound of the formula (I) as hereinbefore defined, wherein

R^1 is methoxymethyl;

R^2 is HET-2;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N

and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 4-, 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring may optionally be oxidised to a S(O) or $S(O)_2$ group, which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano;

R^4 is selected from hydrogen, (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$], (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and HET-2;

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4;

R^7 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-3 is an N-linked, 4, 5 or 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an N-linked, 7 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further heteroatom (in addition to the linking N atom) independently selected from O, S and N, wherein a $-CH_2-$ group can optionally be replaced

by a -C(O)- group and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an 6-10 membered bicyclic saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further nitrogen atom (in addition to the linking N atom) wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-; which ring is optionally substituted on an available carbon or nitrogen atom by 1 substituent selected from hydroxy (not on nitrogen) and R^3;

R^8 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkylamino, di(1-4C)alkylamino, HET-3 (wherein said ring is unsubstituted), (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-4 is a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S;

p is (independently at each occurrence) 0, 1 or 2;

m is 0 or 1;

n is 0, 1 or 2;

provided that when m is 0, then n is 1 or 2;

or a salt, pro-drug or solvate thereof.

It will be understood that when R^4 is $-C(O)NR^5R^5$, each R^5 is independently selected from hydrogen and (1-4C)alkyl, and therefore this definition of R^4 includes (but is not limited to) $-CONH_2$, -CONHMe, $-CONMe_2$ and –CONMeEt.

It will be understood that where a compound of the formula (I) contains more than one HET-2 ring, they may be the same or different.

It will be understood that where a compound of the formula (I) contains more than one group R^4, they may be the same or different.

It will be understood that where a compound of the formula (I) contains more than one group R^5, they may be the same or different.

It will be understood that where a compound of the formula (I) contains more than one group R^8, they may be the same or different.

A similar convention applies for all other groups and substituents on a compound of formula (I) as hereinbefore defined.

It will be understood that any single carbon atom in HET-1 may only be substituted by one group R^6 in order to maintain aromaticity of the ring. Up to two different carbon atoms in a HET-1 ring may be substituted by an R^6 group, each of which may be the same or different, provided the structure thereby formed is stable and aromatic.

It will be understood that R^8 can be present on any or all available carbon atoms in the heterocyclic ring (HET-3) formed by NR^4R^5; each carbon atom can be substituted with 1 or 2 R^8 groups which may be the same or different, provided the structure thereby formed is stable (so, for example, it is not intended to cover gem-dihydroxy substitution). Similarly any available nitrogen atom may be substituted by R^8 provided substitution does not lead to quaternisation of the nitrogen. Preferably, the heterocyclic ring (HET-3) formed by NR^4R^5 is mono-substituted on one nitrogen or carbon atom, or is unsubstituted.

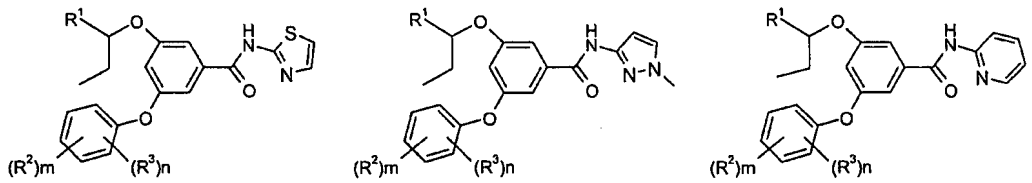
Compounds of Formula (I) may form salts which are within the ambit of the invention. Pharmaceutically acceptable salts are preferred although other salts may be useful in, for example, isolating or purifying compounds.

In another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to a pharmaceutically acceptable salt.

In another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to a pro-drug thereof. Suitable examples of pro-drugs of compounds of formula (I) are in-vivo hydrolysable esters of compounds of formula (I). Therefore in another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to an in-vivo hydrolysable ester thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as *t*-butyl are specific for the branched chain version only. For example,
"(1-4C)alkyl" includes methyl, ethyl, propyl, isopropyl and *t*-butyl. An analogous convention applies to other generic terms.

For the avoidance of doubt, reference to the group HET-1 containing a nitrogen in the 2-position, is intended to refer to the 2-position relative to the amide nitrogen atom to which the group is attached. For example, the following structures are encompassed (but not limiting on the invention):



Suitable examples of HET-1 as a 5- or 6-membered, C-linked heteroaryl ring as hereinbefore defined, include thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl and triazolyl.

It will be understood that HET-2 can be a saturated, or partially or fully unsaturated ring.

Suitable examples of HET-2 include azetidinyl, furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, morpholino, morpholinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, 2-oxo-1,3,4-(4-triazolinyl), 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 1,2,4-triazolyl, 1,2,3-triazolyl, pyranyl, and 4-pyridonyl.

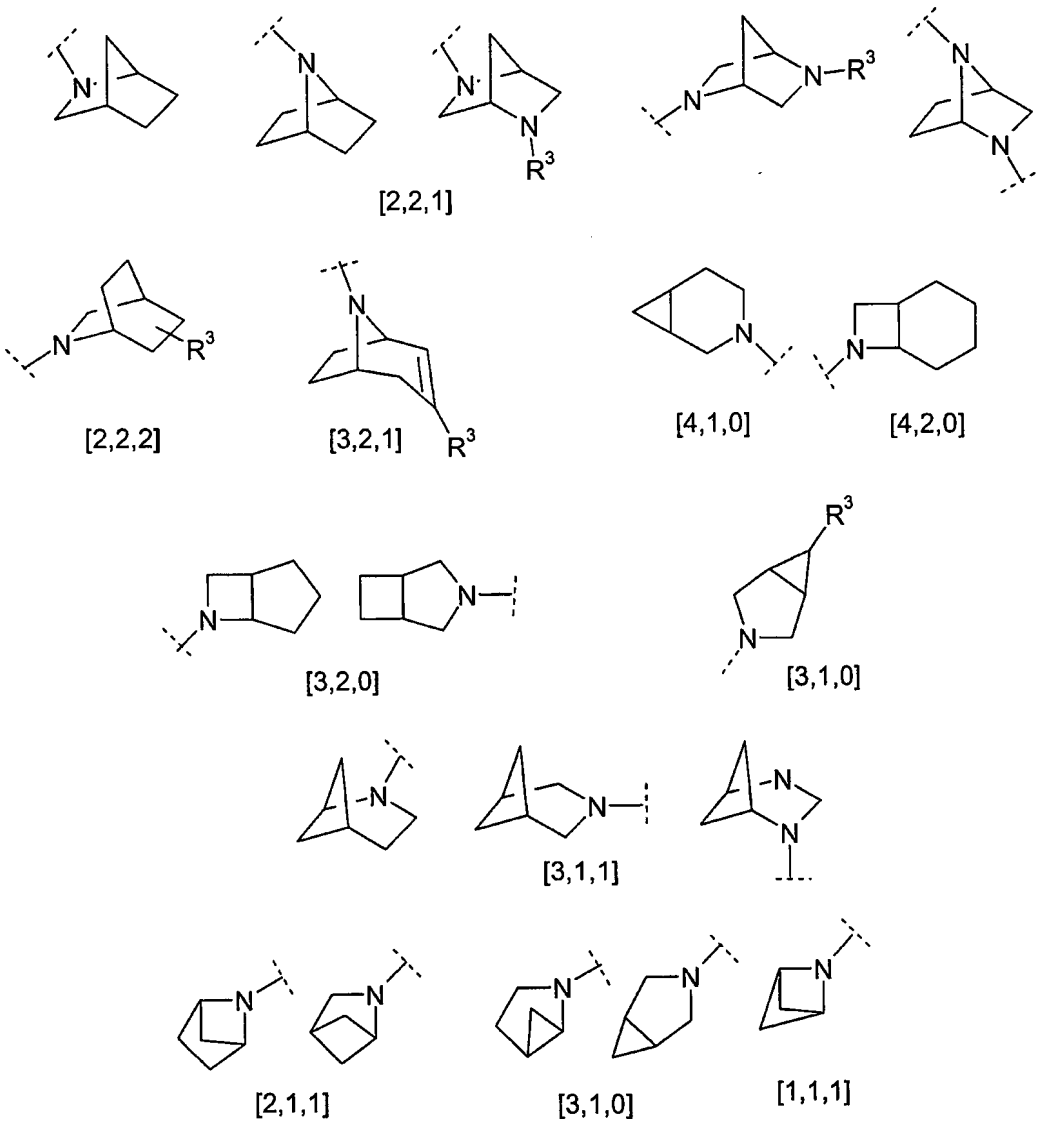
It will be understood that HET-2 may be linked by any appropriate available C or N atom, therefore for example, for HET-2 as "imidazolyl" includes 1- , 2-, 4- and 5-imidazolyl.

Suitable examples of HET-3 as a 4-6 membered saturated or partially unsaturated heterocyclic ring are morpholino, piperidinyl, piperazinyl, pyrrolidinyl and azetidinyl.

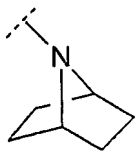
A suitable example of HET-3 as a 7-membered saturated or partially unsaturated heterocyclic ring is homopiperazinyl, homo-morpholino, homo-thiomorpholino (and versions thereof wherein the sulfur is oxidised to an SO or $S(O)_2$ group) and homo-piperidinyl.

Suitable examples of HET-3 as an 6-10 membered bicyclic heterocyclic ring are bicyclic saturated or partially unsaturated heterocyclyl ring such as those illustrated by the

structures shown below (wherein the dotted line indicates the point of attachment to the rest of the molecule):

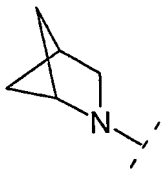


In particular HET-3 is a [2,2,1] system such as



(7-azabicyclo[2.2.1]hept-7-yl).

In another embodiment, HET-3 is a [2.1.1] system such as



(2-azabicyclo[2.1.1]hex-2-yl).

Suitable examples of HET-4 are furyl, pyrrolyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl and triazolyl.

It will be appreciated that, where definitions of heterocyclyl groups HET-1 to HET-4 encompass heteroaryl or heterocyclyl rings which may be substituted on nitrogen, such substitution may not result in charged quaternary nitrogen atoms or unstable structures (such as N-halo compounds). It will be appreciated that the definitions of HET-1 to HET-4 are not intended to include any O-O, O-S or S-S bonds. It will be appreciated that the definitions of HET-1 to HET-4 are not intended to include unstable structures.

Examples of **(1-4C)alkyl** include methyl, ethyl, propyl, isopropyl, butyl and tert-butyl; examples of **(3-6C)cycloalkyl** include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; examples of **halo** include fluoro, chloro, bromo and iodo; examples of **hydroxy(1-4C)alkyl** include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxyisopropyl and 4-hydroxybutyl; examples of **(1-4C)alkoxy(1-4C)alkyl** include methoxymethyl, ethoxymethyl, tert-butoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, methoxypropyl, 2-methoxypropyl and methoxybutyl; examples of **(1-4C)alkylS(O)p(1-4C)alkyl** include methylsulfinylmethyl, ethylsulfinylmethyl, ethylsulfinylethyl, methylsulfinylpropyl, methylsulfinylbutyl, methylsulfonylmethyl, ethylsulfonylmethyl, ethylsulfonylethyl, methylsulfonylpropyl, methylsulfonylbutyl, methylthiomethyl, ethylthiomethyl, ethylthioethyl, methylthiopropyl, and methylthiobutyl; examples of **amino(1-4C)alkyl** include aminomethyl, aminoethyl, 2-aminopropyl, 3-aminopropyl, 1-aminoisopropyl and 4-aminobutyl; examples of **(1-4C)alkylamino(1-4C)alkyl** include (N-methyl)aminomethyl, (N-ethyl)aminomethyl, 1-((N-methyl)amino)ethyl, 2-((N-methyl)amino)ethyl, (N-ethyl)aminoethyl, (N-methyl)aminopropyl, and 4-((N-methyl)amino)butyl; examples of **di(1-4C)alkylamino(1-4C)alkyl** include dimethylaminomethyl, methyl(ethyl)aminomethyl,

methyl(ethyl)aminoethyl, (N,N-diethyl)aminoethyl, (N,N-dimethyl)aminopropyl and (N,N-dimethyl)aminobutyl; examples of **(1-4C)alkylamino** include methylamino, ethylamino, propylamino, isopropylamino, butylamino and tert-butylamino; examples of **di(1-4C)alkylamino** include dimethylamino, methyl(ethyl)amino, diethylamino, dipropylamino, di-isopropylamino and dibutylamino; examples of **–C(O)(1-4C)alkyl** include methylcarbonyl, ethylcarbonyl, propylcarbonyl and tert-butyl carbonyl.

It is to be understood that, insofar as certain of the compounds of Formula (I) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of stimulating GLK directly or inhibiting the GLK/GLKRP interaction. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. It is also to be understood that certain compounds may exist in tautomeric forms and that the invention also relates to any and all tautomeric forms of the compounds of the invention which activate GLK.

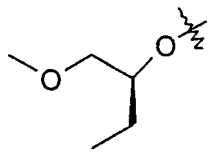
It is also to be understood that certain compounds of the formula (1) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which activate GLK.

In one embodiment of the invention are provided compounds of formula (I), in an alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (I), in a further alternative embodiment are provided in-vivo hydrolysable esters of compounds of formula (I), and in a further alternative embodiment are provided pharmaceutically-acceptable salts of in-vivo hydrolysable esters of compounds of formula (I).

Preferred values of each variable group are as follows. Such values may be used where appropriate with any of the values, definitions, claims, aspects or embodiments defined hereinbefore or hereinafter. In particular, each may be used as an individual limitation on the broadest definition of formula (I). Further, each of the following values

may be used in combination with one or more of the other following values to limit the broadest defintion of formula (I).

(1) R^1 is methoxymethyl and the configuration is preferably (S), that is:



(2) R^2 is $-C(O)NR^4R^5$

(3) R^2 is $-SO_2NR^4R^5$

(4) R^2 is $-S(O)_pR^4$

(5) R^2 is HET-2

(6) m is 1 and R^2 is in the para position relative to the ether linkage

(7) m is 1 and n is 0 or 1

(8) m is 1 and n is 0

(9) m is 1, n is 0 and R^2 is in the para position relative to the ether linkage

(10) m is 1, n is 1, R^2 is in the para position relative to the ether linkage, R^3 is in the ortho position relative to the ether linkage

(11) m is 1, n is 1, R^2 is in the para position relative to the ether linkage, R^3 is in the ortho position relative to the ether linkage

(12) m is 1, n is 1, R^2 is in the para position relative to the ether linkage, R^3 is in the meta position relative to the ether linkage

(13) n is 0

(14) n is 1

(15) n is 2

(16) n is 2 and both R^3 are halo

(17) n is 2 and each R^3 is independently halo or methoxy

(18) m is 1, n is 2 and R^2 is in the para position relative to the ether linkage

(19) m is 1, n is 2, R^2 is in the para position relative to the ether linkage and each R^3 is in an ortho position relative to the ether linkage

(20) m is 1, n is 2, both R^3 are halo, R^2 is in the para position relative to the ether linkage and each R^3 is in an ortho position relative to the ether linkage

(21) m is 1, n is 2, both R^3 are halo, R^2 is in the para position relative to the ether linkage and one R^3 is in an ortho position relative to the ether linkage and the other R^3 is in a meta position relative to the ether linkage

(22) R^3 is fluoromethyl or difluoromethyl

(23) R^3 is halo or trifluoromethyl

(24) R^3 is halo

(25) R^3 is chloro or fluoro

(26) R^3 is fluoro

(27) R^3 is methoxy

(28) n is 2 and both R^3 are fluoro

(29) n is 2 and one R^3 is fluoro and the other is chloro

(30) n is 2, both R^3 are fluoro and are in the 3- and 5-positions (meta-positions) relative to the ether linkage

(31) m is 1, n is 2, R^2 is in the para position relative to the ether linkage, both R^3 are fluoro and are in the 3- and 5-positions relative to the ether linkage

(32) p is 0

(33) p is 1

(34) p is 2

(35) HET-1 is a 5-membered heteroaryl ring

(36) HET-1 is a 6-membered heteroaryl ring

(37) HET-1 is substituted with 1 or 2 substituents independently selected from R^6

(38) HET-1 is substituted with 1 substituent selected from R^6

(39) HET-1 is unsubstituted

(40) HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, and triazolyl

(41) HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl

(42) HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl

(43) HET-1 is selected from thiazolyl, pyrazolyl and oxazolyl

(44) HET-1 is selected from thiadiazolyl and oxadiazolyl

(45) HET-1 is selected from 1,3,4-thiadiazolyl and 1,3,4-oxadiazolyl

(46) HET-1 is selected from 1,2,4-oxadiazolyl and 1,2,4-oxadiazolyl

(47) HET-1 is pyrazolyl, particularly N-methyl or N-ethylpyrazolyl

(48) HET-1 is pyridyl or pyrazinyl

(49) HET-1 is pyrazinyl

(50) HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl;

(51) R^6 is selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4

(52) R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl,
aminomethyl, N-methylaminomethyl, dimethylaminomethyl

(53) R^6 is selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, and di(1-4C)alkylamino(1-4C)alkyl

(54) R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl

(55) R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl and methoxymethyl

(56) R^6 is selected from methyl, ethyl, bromo, chloro and fluoro

(49) R^6 is methyl

(57) R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, dimethylaminomethyl, hydroxymethyl and methoxymethyl

(58) R^6 is selected from methyl, ethyl, aminomethyl, N-methylaminomethyl, dimethylaminomethyl, hydroxymethyl and methoxymethyl

(59) R^6 is selected from (1-4C)alkyl and (1-4C)alkoxy(1-4C)alkyl

(60) R^6 is selected from methyl, ethyl, isopropyl and methoxymethyl

(61) when 2 substituents R^6 are present, both are selected from methyl, ethyl, bromo, chloro and fluoro; preferably both are methyl

(62) R^6 is selected from (1-4C)alkylS(O)p(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4

(63) R^6 is HET-4

(64) HET-4 is selected from furyl, pyrrolyl and thienyl

(65) HET-4 is furyl

(66) R^4 is hydrogen

(67) R^4 is (1-4C)alkyl [substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$]

(68) R^4 is (1-4C)alkyl [substituted by 1 substituent selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$]

(69) R^4 is (1-4C)alkyl

(70) R^4 is (1-4C)alkyl substituted by $-OR^5$

(71) R^4 is (1-4C)alkyl substituted by HET-2

(72) R^4 is (3-6C)cycloalkyl, particularly cyclopropyl or cyclobutyl

(73) R^4 is (3-6C)cycloalkyl substituted by a group selected from R^7

(74) R^4 is (3-6C)cycloalkyl substituted by a group selected from $-OR^5$ and (1-4C)alkyl

(75) R^4 is selected from (1-4C)alkyl and (3-6C)cycloalkyl

(76) R^4 is selected from methyl, ethyl, cyclopropyl and cyclobutyl

(77) R^4 is HET-2

(78) R^4 is selected from hydrogen, (1-4C)alkyl, and (1-4C)alkyl substituted with $-OR^5$

(79) HET-2 is unsubstituted

(80) HET-2 is substituted with 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy and (1-4C)alkoxy

(81) HET-2 is a fully saturated ring system

(82) HET-2 is a fully unsaturated ring system

(83) HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl

(84) HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, thiomorpholinyl, tetrahydrofuranyl, and tetrahydropyranyl

(85) HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl

(86) HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, pyrrolidonyl, 2-oxazolidinonyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl

(87) HET-2 is selected from morpholino, furyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, 2-pyrrolidonyl, 2-oxazolidinonyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl

(88) HET-2 is selected from morpholino, furyl, imidazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, 2-pyrrolidonyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl

(89) HET-2 is oxadiazolyl or pyrazolyl

(90) R^5 is hydrogen

(91) R^5 is (1-4)alkyl, preferably methyl

(92) R^5 is hydrogen or methyl

(93) R^7 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkoxy(1-4C)alkyl, and hydroxy(1-4C)alkyl

(94) R^7 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, and hydroxy(1-4C)alkyl

(95) R^7 is selected from hydroxy, methoxy, -COMe, $-CONH_2$, -CONHMe, $-CONMe_2$, and hydroxymethyl

(96) R^7 is selected from (1-4C)alkyl, hydroxy and (1-4C)alkoxy

(97) R^7 is selected from methyl, ethyl, methoxy and hydroxy

(98) R^8 is selected from methyl, hydroxy, methoxy, -COMe, $-CONH_2$, -CONHMe, $-CONMe_2$, hydroxymethyl, hydroxyethyl, -NHMe and $-NMe_2$(99) R^8 is selected from morpholino, piperidinyl, piperazinyl, pyrrolidinyl and azetidinyl

(100) R^8 is selected from methyl, -COMe, $-CONH_2$, hydroxyethyl and hydroxy

(101) R^8 is selected from (1-4C)alkyl and (1-4C)alkoxy

(102) R^8 is selected from methyl, methoxy and isopropoxy

(103) HET-3 is a fully saturated ring

(104) HET-3 is selected from morpholino, piperidinyl, piperazinyl, pyrrolidinyl and azetidinyl

(105) R^4 and R^5 together with the nitrogen to which they are attached form a ring as defined by HET-3

(106) HET-3 is selected from pyrrolidinyl and azetidinyl

(107) HET-3 is azetidinyl

(108) HET-3 is a 4 to 6-membered saturated or partially unsaturated heterocyclic ring as hereinbefore defined

(109) HET-3 is a 7-membered saturated or partially unsaturated heterocyclic ring as hereinbefore defined

(110) HET-3 is an 6 to 10-membered bicyclic saturated or partially unsaturated heterocyclic ring as hereinbefore defined

(111) HET-3 is 7-azabicyclo[2.2.1]hept-7-yl

(112) HET-3 is 7-azabicyclo[2.2.1]hept-7-yl or 2-azabicyclo[2.1.1]hex-2-yl

(113) HET-3 is selected from morpholino, piperidinyl, piperazinyl, pyrrolidinyl and azetidinyl

(114) HET-3 is unsubstituted

(115) HET-3 is substituted by methyl, methoxy or isopropoxy

According to a further feature of the invention there is provided the following preferred groups of compounds of the invention:

In a futher aspect of the invention there is provided a compound of Formula (I) wherein:

R^1 is methoxymethyl;

R^2 is selected from $-C(O)NR^4R^5$, $-SO_2NR^4R^5$, $-S(O)_pR^4$ and HET-2;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1, 2 or 3 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring may optionally be oxidised to an S(O) or $S(O)_2$ group, which ring is optionally substituted

on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano;

R^4 is selected from hydrogen, (1-4C)alkyl, [optionally substituted by $-OR^5$], (3-6C)cycloalkyl (optionally substituted with 1 group selected from $-OR^5$) and HET-2;

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a 4-6 membered heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4;

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to an S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8;

R^8 is selected from $-OR^5$ and (1-4C)alkyl;

HET-4 is a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S;

p is (independently at each occurrence) 0, 1 or 2;

m is 0 or 1;

n is 0, 1 or 2;

provided that when m is 0, then n is 1 or 2;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention there is provided a compound of Formula (I) wherein:

R^1 is methoxymethyl;

R^2 is selected from $-C(O)NR^4R^5$, $-SO_2NR^4R^5$, $-S(O)_pR^4$ and HET-2;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1, 2 or 3 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring may optionally be oxidised to an S(O) or $S(O)_2$ group, which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano;

R^4 is selected from hydrogen, (1-4C)alkyl, [optionally substituted by $-OR^5$], (3-6C)cycloalkyl (optionally substituted with 1 group selected from $-OR^5$) and HET-2;

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4;

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to an S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an N-linked, 7 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further heteroatom (in addition to the linking N atom) independently selected from O, S and N, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- group and wherein a sulphur atom in the ring may optionally be oxidised to an

S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an 6-10 membered bicyclic saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further nitrogen atom (in addition to the linking N atom), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-; which ring is optionally substituted on an available carbon or nitrogen atom by 1 substituent selected from hydroxy (not on nitrogen) and R^3;

R^8 is selected from $-OR^5$ and (1-4C)alkyl;

HET-4 is a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S;

p is (independently at each occurrence) 0, 1 or 2;

m is 0 or 1;

n is 0, 1 or 2;

provided that when m is 0, then n is 1 or 2;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is a 5- or 6-membered heteroaryl ring as hereinbefore defined;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

HET-2 is a 5- or 6- membered heterocyclyl ring as hereinbefore defined, containing 1 or 2 heteroatoms independently selected from O, N and S; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is a 5- or 6-membered heteroaryl ring and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is an optionally substituted 5- or 6- membered heterocyclyl ring as hereinbefore defined, containing 1 or 2 heteroatoms independently selected from O, N and S; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl, and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$];

R^5 is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-

dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$];

R^5 is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$];

R^5 is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl, and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$];

R^5 is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl and oxadiazolyl, and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is selected from hydrogen, (1-4C)alkyl, [optionally substituted by $-OR^5$], (3-6C)cycloalkyl (optionally substituted with 1 group selected from $-OR^5$) and HET-2;

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from morpholino, furyl, imidazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, 2-pyrrolidonyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl and pyridazinyl, and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is selected from hydrogen, (1-4C)alkyl, [optionally substituted by $-OR^5$], (3-6C)cycloalkyl (optionally substituted with 1 group selected from $-OR^5$) and HET-2;

R^5 is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from morpholino, furyl, imidazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, 2-pyrrolidonyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl and oxadiazolyl, and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is selected from (1-4C)alkyl, [optionally substituted by $-OR^5$], (3-6C)cycloalkyl (optionally substituted with 1 group selected from $-OR^5$) and HET-2;

R^5 is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from piperidinyl, piperazinyl, 3-oxopiperazinyl, 2-pyrrolidonyl, 2,5-dioxopyrrolidinyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 2-oxoimidazolidinyl, and 2,4-dioxoimidazolidinyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl and oxadiazolyl, and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is selected from (1-4C)alkyl [substituted by $-OR^5$], (3-6C)cycloalkyl (optionally substituted with 1 group selected from $-OR^5$) and HET-2;

R^5 is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is piperidinyl or piperazinyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 ;

HET-1 is selected from thiazolyl, thiadiazolyl and pyrazolyl, and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$;

R^4 is piperidinyl, optionally substituted with methyl;

R^5 is hydrogen or methyl;

R^6 is methyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl and pyridazinyl, and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is selected from (1-4C)alkyl, [optionally substituted by -OR^5] and HET-2;

R^5 is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from piperidinyl, piperazinyl, 3-oxopiperazinyl, 2-pyrrolidonyl, 2,5-dioxopyrrolidinyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 2-oxoimidazolidinyl, and 2,4-dioxoimidazolidinyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl and pyridazinyl, and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is selected from (1-4C)alkyl [substituted by -OR^5], (3-6C)cycloalkyl (optionally substituted with 1 group selected from -OR^5) and HET-2;

R^5 is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is piperidinyl or piperazinyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl and oxadiazolyl, and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 and R^5 together with the nitrogen to which they are attached form a morpholino, piperidinyl, piperazinyl, pyrrolidinyl or azetidinyl ring, which ring is optionally substituted on a carbon or nitrogen atom by R^8;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

R^8 is selected from hydroxy, (1-4C)alkoxy and (1-4C)alkyl

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl and oxadiazolyl, and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 and R^5 together with the nitrogen to which they are attached form a morpholino, piperidinyl, piperazinyl, pyrrolidinyl or azetidinyl ring, which ring is optionally substituted on a carbon or nitrogen atom by R^8;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

R^8 is pyrrolidine or piperidine;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl and oxadiazolyl, and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 and R^5 together with the nitrogen to which they are attached form a morpholino, piperidinyl, piperazinyl, pyrrolidinyl or azetidinyl ring, which ring is optionally substituted on a carbon or nitrogen atom by (1-4C)alkyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl and pyridazinyl, and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 and R^5 together with the nitrogen to which they are attached form a morpholino, piperidinyl, piperazinyl, pyrrolidinyl or azetidinyl ring, which ring is optionally substituted on a carbon or nitrogen atom by (1-4C)alkyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0;

HET-1 is selected from thiazolyl, thiadiazolyl and pyrazolyl, and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together with the nitrogen to which they are attached form a piperidinyl, or piperazinyl ring, which ring is optionally substituted on a carbon or nitrogen atom by (1-4C)alkyl or by a pyrrolidinyl ring;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0;

HET-1 is selected from thiazolyl, thiadiazolyl and pyrazolyl, and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together with the nitrogen to which they are attached form an azetidinyl ring which ring is optionally substituted on a carbon atom by hydroxy;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 1;

HET-1 is selected from thiazolyl, thiadiazolyl and pyrazolyl, and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$;

R^3 is chloro or fluoro;

R^4 and R^5 together with the nitrogen to which they are attached form an azetidinyl ring which ring is optionally substituted on a carbon atom by hydroxy;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0;

HET-1 is selected from thiazolyl, thiadiazolyl and pyrazolyl, and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together with the nitrogen to which they are attached form a 7-membered ring HET-3 which ring is optionally substituted on a carbon or nitrogen atom by methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0;

HET-1 is selected from thiazolyl, thiadiazolyl and pyrazolyl, and is optionally substituted by a group R^6;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together with the nitrogen to which they are attached form an optionally substituted 6-10 membered bicyclic heterocyclic ring HET-3;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is a 5- or 6-membered heteroaryl ring as herebefore defined;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$];

R^5 is hydrogen or methyl;

HET-2 is a 5- or 6- membered heterocyclyl ring as hereinbefore defined, containing 1 or 2 heteroatoms independently selected from O, N and S; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is a 5- or 6-membered heteroaryl ring, and is optionally substituted by a group R^6;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$];

R^5 is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is a 5- or 6- membered heterocyclyl ring as hereinbefore defined, containing 1 or 2 heteroatoms independently selected from O, N and S; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl and is optionally substituted by a group R^6;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$];

R^5 is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl and is optionally substituted by a group R^6;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is selected from hydrogen, (1-4C)alkyl, [optionally substituted by $-OR^5$], (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and HET-2;

R^5 is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl and is optionally substituted by a group R^6;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$];

R^5 is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl and is optionally substituted by a group R^6;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is selected from hydrogen, (1-4C)alkyl, [optionally substituted by -OR^5], (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and HET-2;

R^5 is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is selected from –OR^5 and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl and is optionally substituted by a group R^6;

R^2 is –S(O)pR^4;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0;

HET-1 is selected from thiazolyl, thiadiazolyl and pyrazolyl and is optionally substituted by a group R^6;

R^2 is –S(O)pR^4;

p is 1 or 2;

R^4 is (1-4C)alkyl;

R^6 is methyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0;

HET-1 is selected from thiazolyl, thiadiazolyl and pyrazolyl and is optionally substituted by a group R^6;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^4 is (3-6C)cycloalkyl;

R^6 is methyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl and is optionally substituted by a group R^6;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is a 5- or 6-membered heteroaryl ring as hereinbefore defined;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^5 is hydrogen or (1-4C)alkyl;

HET-2 is a 5- or 6- membered heterocyclyl ring as hereinbefore defined, containing 1 or 2 heteroatoms independently selected from O, N and S; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl and is optionally substituted by a group R^6;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^5 is hydrogen or methyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl and is optionally substituted by a group R^6;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^5 is hydrogen or methyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl and is optionally substituted by a group R^6;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^5 is hydrogen or methyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl and is optionally substituted by a group R^6;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^5 is hydrogen or methyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl and is optionally substituted by a group R^6;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl and is optionally substituted by a group R^6;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl and is optionally substituted by a group R^6;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl and is optionally substituted by a group R^6;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; wherein HET-2 is optionally substituted by a group R^7; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention there is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is 3-pyrazolyl, substituted on a nitrogen atom by methyl or ethyl;

R^2 is selected from dimethylaminocarbonyl, N-azetidinylcarbonyl, N-pyrrolidinylcarbonyl, methylsulfonyl and ethylsulfonyl;

R^3 is fluoro or chloro;

or a salt, pro-drug or solvate thereof.

Further preferred compounds of the invention are each of the Examples, each of which provides a further independent aspect of the invention. In further aspects, the present invention also comprises any two or more compounds of the Examples.

In one aspect, particular compounds of the invention comprise any one or more of:

3-fluoro-4-(3-{[(1S)-1-(methoxymethyl)propyl]oxy}-5-{[(1-methyl-1H-pyrazol-3-yl)amino]carbonyl}phenoxy)-N,N-dimethylbenzamide;

3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-{[(1S)-1-(methoxymethyl)propyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide; and

3-[4-(azetidin-1-ylcarbonyl)-2-chlorophenoxy]-5-{[(1S)-1-(methoxymethyl)propyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

or a salt, pro-drug or solvate thereof.

In another aspect, particular compounds of the invention comprise any one or more of:

3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-{[(1S)-1-(methoxymethyl)propyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide; and

3-[4-(azetidin-1-ylcarbonyl)-2-chlorophenoxy]-5-{[(1S)-1-(methoxymethyl)propyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

or a salt, pro-drug or solvate thereof.

The compounds of the invention may be administered in the form of a pro-drug. A pro-drug is a bioprecursor or pharmaceutically acceptable compound being degradable in the body to produce a compound of the invention (such as an ester or amide of a compound of the invention, particularly an in-vivo hydrolysable ester). Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen;

c) H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

f) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

The contents of the above cited documents are incorporated herein by reference.

Examples of pro-drugs are as follows. An in-vivo hydrolysable ester of a compound of the invention containing a carboxy or a hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include C_1 to C_6alkoxymethyl esters for example methoxymethyl, C_1 to C_6alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_3 to C_8cycloalkoxycarbonyloxyC_1 to C_6alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters.

An in-vivo hydrolysable ester of a compound of the invention containing a

hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. It will be understood that an acid addition salt may be formed with any sufficiently basic group which may for example be in HET-1 or may for example be a substituent R^2. In addition a suitable pharmaceutically-acceptable salt of a benzoxazinone derivative of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

A further feature of the invention is a pharmaceutical composition comprising a compound of Formula (I) as defined above, or a salt, solvate or prodrug thereof, together with a pharmaceutically-acceptable diluent or carrier.

According to another aspect of the invention there is provided a compound of Formula (I) as defined above for use as a medicament.

Further according to the invention there is provided a compound of Formula (I) for use in the preparation of a medicament for treatment of a disease mediated through GLK, in particular type 2 diabetes.

The compound is suitably formulated as a pharmaceutical composition for use in this way.

According to another aspect of the present invention there is provided a method of treating GLK mediated diseases, especially diabetes, by administering an effective amount of a compound of Formula (I) or salt, solvate or pro-drug thereof, to a mammal in need of such treatment.

Specific diseases which may be treated by a compound or composition of the invention include: blood glucose lowering in Type 2 Diabetes Mellitus without a serious risk of hypoglycaemia (and potential to treat type 1), dyslipidemia, obesity, insulin resistance, metabolic syndrome X, impaired glucose tolerance.

As discussed above, thus the GLK/GLKRP system can be described as a potential "Diabesity" target (of benefit in both Diabetes and Obesity). Thus, according to another aspect of the invention there if provided the use of a compound of Formula (I) or salt, solvate or pro-drug thereof, in the preparation of a medicament for use in the combined treatment or prevention of diabetes and obesity.

According to another aspect of the invention there if provided the use of a compound of Formula (I) or salt, solvate or pro-drug thereof, in the preparation of a medicament for use in the treatment or prevention of obesity.

According to a further aspect of the invention there is provided a method for the combined treatment of obesity and diabetes by administering an effective amount of a compound of Formula (I) or salt, solvate or pro-drug thereof, to a mammal in need of such treatment.

According to a further aspect of the invention there is provided a method for the treatment of obesity by administering an effective amount of a compound of Formula (I) or salt, solvate or pro-drug thereof, to a mammal in need of such treatment.

Compounds of the invention may be particularly suitable for use as pharmaceuticals, for example because of favourable physical and/or pharmacokinetic properties and/or toxicity profile and/or potency.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration

(for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing). Generally, a dosage form suitable for oral use is preferred.

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from

fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile

injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula (I) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula (I) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

The elevation of GLK activity described herein may be applied as a sole therapy or in combination with one or more other substances and/or treatments for the indication being treated. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For example in the treatment of diabetes mellitus, chemotherapy may include the following main categories of treatment:

1) Insulin and insulin analogues;

2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide), prandial glucose regulators (for example repaglinide, nateglinide);

3) Agents that improve incretin action (for example dipeptidyl peptidase IV inhibitors, and GLP-1 agonists);

4) Insulin sensitising agents including PPARgamma agonists (for example pioglitazone and rosiglitazone), and agents with combined PPARalpha and gamma activity;

5) Agents that modulate hepatic glucose balance (for example metformin, fructose 1, 6 bisphosphatase inhibitors, glycogen phopsphorylase inhibitors, glycogen synthase kinase inhibitors);

6) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);

7) Agents that prevent the reabsorption of glucose by the kidney (SGLT inhibitors);

8) Agents designed to treat the complications of prolonged hyperglycaemia (for example aldose reductase inhibitors);

9) Anti-obesity agents (for example sibutramine and orlistat);

10) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (eg statins); PPARα agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); bile acid absorption inhibitors (IBATi) and nicotinic acid and analogues (niacin and slow release formulations);

11) Antihypertensive agents such as, β blockers (eg atenolol, inderal); ACE inhibitors (eg lisinopril); Calcium antagonists (eg. nifedipine); Angiotensin receptor antagonists (eg candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);

12) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors); antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin;

13) Agents which antagonise the actions of glucagon; and

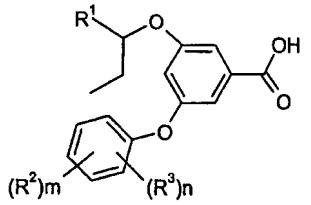
14) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (eg. aspirin) and steroidal anti-inflammatory agents (eg. cortisone).

According to another aspect of the present invention there is provided individual compounds produced as end products in the Examples set out below and salts, solvates and pro-drugs thereof.

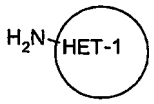
A compound of the invention, or a salt thereof, may be prepared by any process known to be applicable to the preparation of such compounds or structurally related compounds. Functional groups may be protected and deprotected using conventional methods. For examples of protecting groups such as amino and carboxylic acid protecting groups (as well as means of formation and eventual deprotection), see T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", Second Edition, John Wiley & Sons, New York, 1991.

Processes for the synthesis of compounds of Formula (I) are provided as a further feature of the invention. Thus, according to a further aspect of the invention there is provided a process for the preparation of a compound of Formula (I), which comprises a process a) to e) (wherein the variables are as defined hereinbefore for compounds of Formula (I) unless otherwise defined):

(a) reaction of an acid of Formula (III) or activated derivative thereof with a compound of Formula (IV), wherein R^1 is methoxymethyl or a protected version thereof;



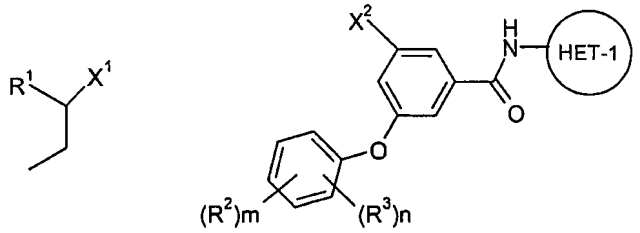
(III)



(IV);

or

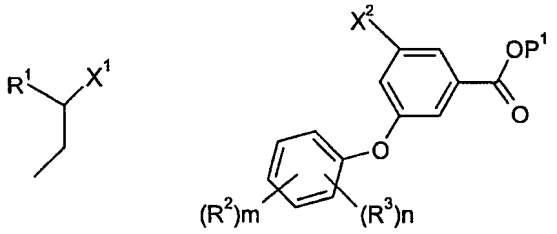
(b) reaction of a compound of Formula (V) with a compound of Formula (VI),



(V) (VI)

wherein X^1 is a leaving group and X^2 is a hydroxyl group or X^1 is a hydroxyl group and X^2 is a leaving group, and wherein R^1 is methoxymethyl or a protected version thereof;

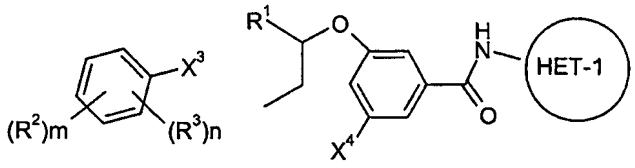
process (b) could also be accomplished using the intermediate ester Formula (VII), wherein P^1 is a protecting group as hereinafter described, followed by ester hydrolysis and amide formation by procedures described elsewhere and well known to those skilled in the art;



(V) (VII)

or

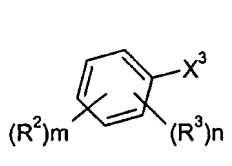
(c) reaction of a compound of Formula (VIII) with a compound of Formula (IX)



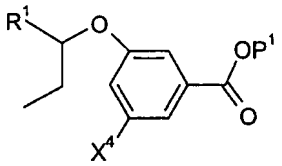
(VIII) (IX)

wherein X^3 is a leaving group or an organometallic reagent and X^4 is a hydroxyl group or X^3 is a hydroxyl group and X^4 is a leaving group or an organometallic reagent, and wherein R^1 is methoxymethyl or a protected version thereof;

process (c) could also be accomplished using the intermediate ester Formula (X), followed by ester hydrolysis and amide formation by procedures described elsewhere and well known to those skilled in the art;



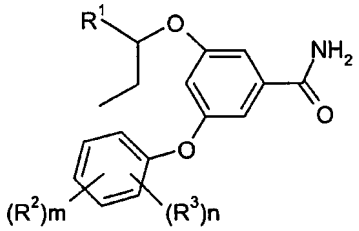
(VIII)



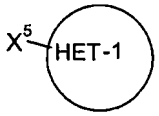
(X)

or

(d) reaction of a compound of Formula (XI) with a compound of Formula (XII),



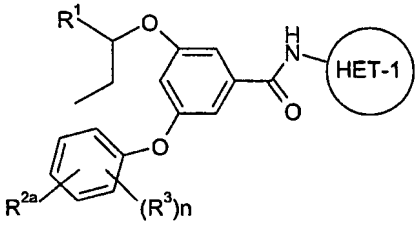
(XI)



(XII);

wherein X^5 is a leaving group; and wherein R^1 is methoxymethyl or a protected version thereof; or

e) reaction of a compound of formula (XIII)



(XIII)

wherein R^{2a} is a precursor to R^2, such as a carboxylic acid, ester or anhydride (for R^2 = $-CONR^4R^5$) or the sulfonic acid equivalents (for R^2 is $-SO^2NR^4R^5$); with an amine of formula $-NR^4R^5$;

and thereafter, if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a salt, pro-drug or solvate thereof.

Suitable leaving groups X^1 to X^5 for processes b) to d) are any leaving group known in the art for these types of reactions, for example halo, alkoxy, trifluoromethanesulfonyloxy,

methanesulfonyloxy, or p-toluenesulfonyloxy; or a group (such as a hydroxy group) that may be converted into a leaving group (such as an oxytriphenylphosphonium group) *in situ*.

Suitable values for R^1 as a protected hydroxy group are any suitable protected hydroxy group known in the art, for example simple ethers such as a methyl ether, or silylethers such as $-OSi[(1\text{-}4C)alkyl]_3$ (wherein each (1-4C)alkyl group is independently selected from methyl, ethyl, propyl, isopropyl, and tertbutyl). Examples of such trialkylsilyl groups are trimethylsilyl, triethylsilyl, triisopropylsilyl and tert-butyldimethylsilyl. Further suitable silyl ethers are those containing phenyl and substituted phenyl groups, such as $-Si(PhMe_2)$ and $-Si(TolMe_2)$ (wherein Tol = methylbenzene). Further suitable values for hydroxy protecting groups are given hereinafter.

Compounds of Formulae (III) to (XII) are commercially available, or are known in the art, or may be made by processes known in the art, for example as shown in the accompanying Examples. For further information on processes for making such compounds, we refer to our PCT publications WO 03/000267, WO 03/015774 and WO 03/000262 and references therein. In general it will be appreciated that any aryl-O or alkyl-O bond may be formed by nucleophilic substitution or metal catalysed processes, optionally in the presence of a suitable base.

Compounds of Formula (XIII) may be made by processes such as those shown in processes a) to d) and/or by those processes mentioned above for compounds of formulae (III) to (XII).

Examples of conversions of a compound of Formula (I) into another compound of Formula (I), well known to those skilled in the art, include functional group interconversions such as hydrolysis, hydrogenation, hydrogenolysis, oxidation or reduction, and/or further functionalisation by standard reactions such as amide or metal-catalysed coupling, or nucleophilic displacement reactions. An example would be removal of an R^3=chloro substituent, for example by reaction with hydrogen at atmospheric or elevated pressure, in a suitable solvent such as THF/methanol or ethanol.

It will be understood that substituents R^8, R^6 and/or R^7 may be introduced into the molecule at any convenient point in the synthetic sequence or may be present in the starting materials. A precursor to one of these substituents may be present in the molecule during the

process steps a) to e) above, and then be transformed into the desired substituent as a final step to form the compound of formula (I); followed where necessary by

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a salt or pro-drug thereof.

Specific reaction conditions for the above reactions are as follows, wherein when P^1 is a protecting group P^1 is preferably C_{1-4}alkyl, for example methyl or ethyl:

Process a) – coupling reactions of amino groups with carboxylic acids to form an amide are well known in the art. For example,

(i) using an appropriate coupling reaction, such as a carbodiimide coupling reaction performed with EDAC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) in the presence of dimethylaminopyridine (DMAP) in a suitable solvent such as dichloromethane (DCM), chloroform or dimethylformamide (DMF) at room temperature; or

(ii) reaction in which the carboxylic group is activated to an acid chloride by reaction with oxalyl chloride in the presence of a suitable solvent such as DCM. The acid chloride can then be reacted with a compound of Formula (IV) in the presence of a base, such as triethylamine or pyridine, in a suitable solvent such as DCM or pyridine at a temperature between 0°C and 80°C.

Process b) – compounds of Formula (V) and (VI) can be reacted together in a suitable solvent, such as DMF or tetrahydrofuran (THF), with a base such as sodium hydride or potassium *tert*-butoxide, at a temperature in the range 0 to 200°C, optionally using microwave heating or metal catalysis such as palladium(II)acetate, palladium on carbon, copper(II)acetate or copper(I)iodide; alternatively, compounds of Formula (V) and (VI) can be reacted together in a suitable solvent, such as THF or DCM, with a suitable phosphine such as triphenylphosphine, and azodicarboxylate such as diethylazodicarboxylate; process b) could also be carried out using a precursor to the ester of formula (VII) such as an aryl-nitrile or trifluoromethyl derivative, followed by conversion to a carboxylic acid and amide formation as previously described;

Process c) - compounds of Formula (VIII) and (IX) can be reacted together in a suitable solvent, such as DMF or THF, with a base such as sodium hydride or potassium tert-butoxide, at a temperature in the range 0 to 200°C, optionally using microwave heating

or metal catalysis such as palladium(II)acetate, palladium on carbon, copper(II)acetate or copper(I)iodide; process c) could also be carried out using a precursor to the ester of formula (X) such as an aryl-nitrile or trifluoromethyl derivative, followed by conversion to a carboxylic acid and amide formation as previously described;

compounds of the formula (VIII) are commercially available or can be prepared from commercially available materials by processes well known to those skilled in the art, for example functional group interconversions (such as hydrolysis, hydrogenation, hydrogenolysis, oxidation or reduction), and/or further functionalisation and/or cyclisation by standard reactions (such as amide or sulphonamide or metal-catalysed coupling, or nucleophilic displacement or electrophilic substitution reactions);

Process d) – reaction of a compound of Formula (XI) with a compound of Formula (XII) can be performed in a polar solvent, such as DMF or a non-polar solvent such as THF with a strong base, such as sodium hydride or potassium *tert*-butoxide at a temperature between 0 and 200°C, optionally using microwave heating or metal catalysis, such as palladium(II)acetate, palladium on carbon, copper(II)acetate or copper(I)iodide;

Process e) - coupling reactions of amino groups with carboxylic or sulfonic acids or acid derivatives to form an amide are well known in the art and are described above for Process a).

Certain intermediates of formula (III), (VI), (VII), (IX) and/or (XI) are believed to be novel and comprise an independent aspect of the invention.

Certain intermediates of formula (III), (IX) and/or (XI) wherein R^1 is methoxymethyl, or a trialkylsilylether are believed to be novel and comprise an independent aspect of the invention.

Certain intermediates of formula (XIII) are believed to be novel and comprise an independent aspect of the invention.

During the preparation process, it may be advantageous to use a protecting group for a functional group within the molecule. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (e.g. isopropyl, t-butyl); lower alkoxy lower alkyl groups (e.g. methoxymethyl, ethoxymethyl, isobutoxymethyl; lower aliphatic acyloxy lower alkyl groups, (e.g. acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (e.g. 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (e.g. p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (e.g. trimethylsilyl and t-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (e.g. trimethylsilylethyl); and (2-6C)alkenyl groups (e.g. allyl and vinylethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed hydrolysis. Hydrogenation may also be used.

Examples of hydroxy protecting groups include methyl, lower alkenyl groups (e.g. allyl); lower alkanoyl groups (e.g. acetyl); lower alkoxycarbonyl groups (e.g. t-butoxycarbonyl); lower alkenyloxycarbonyl groups (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzoyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); tri lower alkyl/arylsilyl groups (e.g. trimethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl); aryl lower alkyl groups (e.g. benzyl) groups; and triaryl lower alkyl groups (e.g. triphenylmethylExamples of amino protecting groups include formyl, aralkyl groups (e.g. benzyl and substituted benzyl, e.g. p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (e.g. t-butoxycarbonyl); lower alkenyloxycarbonyl (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl,

p-nitrobenzyloxycarbonyl; trialkylsilyl (e.g. trimethylsilyl and t-butyldimethylsilyl); alkylidene (e.g. methylidene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base, metal- or enzymically-catalysed hydrolysis, or photolytically for groups such as o-nitrobenzyloxycarbonyl, or with fluoride ions for silyl groups, or catalytic hydrogenation. For example, methylether protecting groups for hydroxy groups may be removed by trimethylsilyliodide. A tert-butyl ether protecting group for a hydroxy group may be removed by hydrolysis, for example by use of hydrochloric acid in methanol.

Examples of protecting groups for amide groups include aralkoxymethyl (e.g. benzyloxymethyl and substituted benzyloxymethyl); alkoxymethyl (e.g. methoxymethyl and trimethylsilylethoxymethyl); tri alkyl/arylsilyl (e.g. trimethylsilyl, t-butyldimethylsily, t-butyldiphenylsilyl); tri alkyl/arylsilyloxymethyl (e.g. t-butyldimethylsilyloxymethyl, t-butyldiphenylsilyloxymethyl); 4-alkoxyphenyl (e.g. 4-methoxyphenyl); 2,4-di(alkoxy)phenyl (e.g. 2,4-dimethoxyphenyl); 4-alkoxybenzyl (e.g. 4-methoxybenzyl); 2,4-di(alkoxy)benzyl (e.g. 2,4-di(methoxy)benzyl); and alk-1-enyl (e.g. allyl, but-1-enyl and substituted vinyl e.g. 2-phenylvinyl).

Aralkoxymethyl, groups may be introduced onto the amide group by reacting the latter group with the appropriate aralkoxymethyl chloride, and removed by catalytic hydrogenation. Alkoxymethyl, tri alkyl/arylsilyl and tri alkyl/silyloxymethyl groups may be introduced by reacting the amide with the appropriate chloride and removing with acid; or in the case of the silyl containing groups, fluoride ions. The alkoxyphenyl and alkoxybenzyl groups are conveniently introduced by arylation or alkylation with an appropriate halide and removed by oxidation with ceric ammonium nitrate. Finally alk-1-enyl groups may be introduced by reacting the amide with the appropriate aldehyde and removed with acid.

The following examples are for illustration purposes and are not intended to limit the scope of this application. Each exemplified compound represents a particular and independent aspect of the invention. In the following non-limiting examples, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at room temperature, that is in the range 18-25 °C and under an atmosphere of an inert gas such as argon or nitrogen unless otherwise stated;

(iii) yields are given for illustration only and are not necessarily the maximum attainable;

(iv) the structures of the end-products of the Formula (I) were confirmed by nuclear (generally proton) magnetic resonance (NMR) with a field strength (for proton) of 300MHz (generally using a Varian Gemini 2000) or 400 MHz (generally using a Bruker Avance DPX400), unless otherwise stated, and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis

(vi) Purification by chromatography generally refers to flash column chromatography, on silica unless otherwise stated. Column chromatography was generally carried out using prepacked silica cartridges (from 4g up to 400g) such as Redisep™ (available, for example, from Presearch Ltd, Hitchin, Herts, UK) or Biotage (Biotage UK Ltd, Hertford, Herts, UK), eluted using a pump and fraction collector system. Purification by Solid Phase Extraction (SPE) methods generally refers to the use of chromatography cartridges packed with SPE materials such as ISOLUTE® SCX-2 columns (available, for example, From International Sorbent Technology Ltd, Dryffryn Business Park, Hengoed, Mid Glamorgan, UK);

(vii) Mass spectra (MS) data was generated on an LCMS system where the HPLC component comprised generally either a Agilent 1100 or Waters Alliance HT (2790 & 2795) equipment and was run on a Phemonenex Gemini C18 5μm, 50 x 2 mm column (or similar) eluting with either acidic eluent (for example, using a gradient between 0 – 95% water / acetonitrile with 5% of a 1% formic acid in 50:50 water:acetonitrile (v/v) mixture; or using an equivalent solvent system with methanol instead of acetonitrile), or basic eluent (for example, using a gradient between 0 – 95% water / acetonitrile with 5% of a 0.1% 880 Ammonia in acetonitrile mixture); and the MS component comprised generally a Waters

ZQ spectrometer. Chromatograms for Electrospray (ESI) positive and negative Base Peak Intensity, and UV Total Absorption Chromatogram from 220-300nm, are generated and values for m/z are given; generally, only ions which indicate the parent mass are reported and unless otherwise stated the value quoted is $(M-H)^-$;

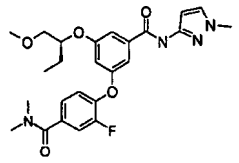
(viii) Suitable microwave reactors include "Smith Creator", "CEM Explorer", "Biotage Initiator sixty" and "Biotage Initiator eight".

Abbreviations

$CDCl_3$	deuterochloroform;
DCM	dichloromethane;
DEAD	diethylazodicarboxylate;
DIAD	diisopropylazodicarboxylate;
DIPEA	*N,N*-Diisopropylethylamine;
DMSO	dimethyl sulfoxide;
DMF	dimethylformamide;
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate;
HPLC	high pressure liquid chromatography
HPMC	hydroxypropylmethylcellulose;
LCMS	liquid chromatography / mass spectroscopy;
NMR	nuclear magnetic resonance spectroscopy;
pH	$-\log_{10}$[hydrogen ion]
RT	room temperature;
THF	tetrahydrofuran;
TFA	trifluoroacetic acid

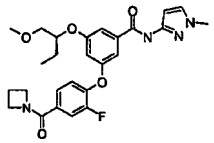
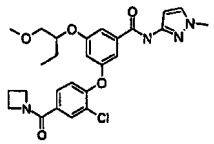
All compound names were derived using ACD NAME computer package.

Example 1: 3-Fluoro-4-(3-{[(1*S*)-1-(methoxymethyl)propyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenoxy)-*N*,*N*-dimethylbenzamide

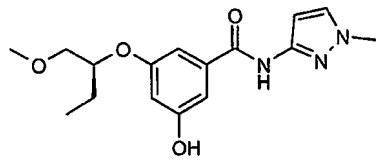


Potassium carbonate (276 mg)was added to a solution of 3-hydroxy-5-{[(1*S*)-1-(methoxymethyl)propyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (**Intermediate 1**, 319 mg) and 3,4-difluoro-*N*,*N*-dimethylbenzamide (**Intermediate 7**, 204 mg) in acetonitrile (3.5 mL) and the stirred mixture subjected to microwave heating at 180°C for 4 h. The mixture allowed to return to ambient temperature and pressure, the acetonitrile evaporated, and the residue chromatographed on silica (eluting with 0-5% methanol in ethyl acetate) to give the desired compound (105 mg). ^{1}H NMR δ (d_6-DMSO): 0.91 (t,3H), 1.64 (m, 2H), 2.96 (s, 6H), 3.26 (s, 3H), 3.50 (d, 2H), 3.76 (s, 3H), 4.54 (m, 1H), 6.55 (d, 1H), 6.82 (m, 1H), 7.16 (s, 1H), 7.25 (m, 2H), 7.42 (s, 1H), 7.47 (d, 1H), 7.58 (m, 1H), 10.83 (br s, 1H); *m/z* 485 $(M+H)^+$

In a similar manner the following analogues were prepared:

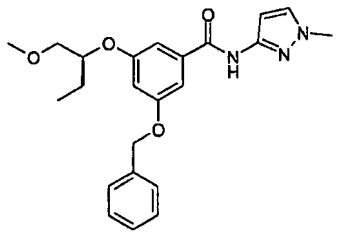
Example	Structure	*m/z*	^{1}H NMR : δ (d_6-DMSO)
2		497 $(M+H)^+$	0.92 (t, 3H), 1.63 (m, 2H), 2.24 (m, 2H), 3.25 (s, 3H), 3.49 (d, 2H), 3.75 (s, 3H), 4.04 (br s, 2H), 4.34 (br s, 2H), 4.55 (m, 1H), 6.53 (d, 1H), 6.83 (m, 1H), 7.14 (m, 1H), 7.22 (t, 1H), 7.42 (m, 1H), 7.47 (d, 1H), 7.56 (m, 1H), 7.61 (dd, 1H), 10.82 (br s, 1H)
3		513 $(M+H)^+$	0.91 (t, 3H), 1.63 (m, 2H), 2.24 (m, 2H), 3.25 (s, 3H), 3.50 (d, 2H), 3.76 (s, 3H), 4.04 (br s, 2H), 4.34 (br s, 2H), 4.55 (m, 1H), 6.52 (d, 1H), 6.82 (t, 1H), 7.12 (m, 2H), 7.43 (m, 1H), 7.58 (m, 2H), 7.79 (d, 1H), 10.82 (brs, 1H)

Intermediate 1: 3-Hydroxy-5-{[(1*S*)-1-(methoxymethyl)propyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



10% w/w Palladium on carbon (450 mg) was added to a solution of 3-(benzyloxy)-5-{[(1*S*)-1-(methoxymethyl)propyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (**Intermediate 2,** 4.6 g, 11 mmol) in THF (50 mL) and methanol (50 mL) and the resulting mixture stirred under an atmosphere of hydrogen for 6 hours. The mixture was filtered and evaporated to afford the title compound as a white solid (3.6 g 100%). ^{1}H NMR δ ($CDCl_3$): 0.95 (t, 3H), 1.6-1.8 (m, 2H), 3.4 (s, 3H), 3.55 (m, 2H), 3.8 (s, 3H), 4.3 (m, 1H), 6.65 (s, 1H), 6.8 (s, 1H), 7.0 (m, 2H), 7.2 (m, 1H), 7.3 (s, 1H), 8.7 (s, 1H), *m/z* 320 $(M+H)^+$

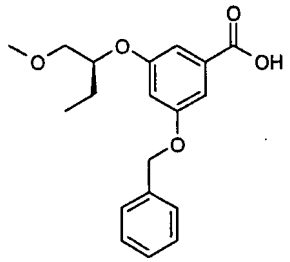
Intermediate 2: 3-(Benzyloxy)-5-{[(1*S*)-1-(methoxymethyl)propyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



HATU (8.53 g, 22.4 mmol) was added to a solution of 3-(benzyloxy)-5-{[(1*S*)-1-(methoxymethyl)propyl]oxy}benzoic acid (**Intermediate 3,** 4.75 g, 14.4 mmol) and 3-amino-1-methyl-1*H*-pyrazole (2.04 g, 21 mmol) in DMF (25 mL) followed by the addition of DIPEA (7.0 mL, 40 mmol) and the resulting mixture was stirred for 16 hours. The mixture was partitioned between ethyl acetate (100 mL) and water (30 mL). The organic layer was separated, washed with 1N citric acid (30 mL), water (30 mL), saturated sodium bicarbonate (30 mL), water (30 mL) and brine (30 mL) then dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (eluting with 50% ethyl acetate in isohexane) to give the title compound (4.57 g, 85%) as a colourless oil ^{1}H NMR δ ($CDCl_3$): 0.95 (t, 3H), 1.6-1.8 (m, 2H), 3.4 (s, 3H), 3.55 (m, 2H), 3.8 (s, 3H), 4.3 (m,

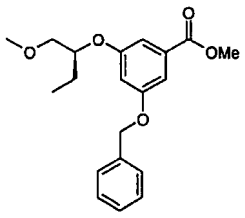
1H), 5.05 (s, 2H), 6.75 (s, 1H), 6.8 (s, 1H), 7.05 (d, 2H), 7.25 (s, 1H), 7.4 (m, 5H), 8.45 (s, 1H), *m/z* 410 $(M+H)^+$

Intermediate 3: 3-(Benzyloxy)-5-{[(1*S*)-1-(methoxymethyl)propyl]oxy}benzoic acid



1N Lithium hydroxide solution in water (40 mL, 40 mmol) was added to a solution of methyl 3-(benzyloxy)-5-{[(1*S*)-1-(methoxymethyl)propyl]oxy}benzoate (**Intermediate 4,** 6.85 g, 20 mmol) in THF (75 mL) and methanol (25 mL), a further 100 mL water was added portionwise over 2 hours with stirring. The organic solvents were removed by evaporation and the cloudy solution filtered. The pH of the filtrate was adjusted to 3 by the addition of 2 M hydrochloric acid. This was extracted with ethyl acetate (3×70 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford the title compound as a colourless oil which solidified (6.36 g, 96%). ^1H NMR δ ($CDCl_3$): 0.95 (t, 3H), 1.6-1.8 (m, 2H), 3.4 (s, 3H), 3.55 (m, 2H), 4.3 (m, 1H), 5.05 (s, 2H), 6.8 (s, 1H), 7.3-7.5 (m, 7H), *m/z* 329 $(M-H)^-$

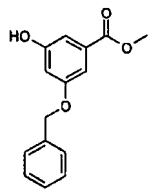
Intermediate 4: Methyl 3-(benzyloxy)-5-{[(1*S*)-1-(methoxymethyl)propyl]oxy}benzoate



A solution of 40% DEAD in toluene (15.8 mL, 36.25 mmol) was added dropwise over 30 minutes to a stirred solution of methyl 3-(benzyloxy)-5-hydroxybenzoate (**Intermediate 5,** 7.5 g, 29 mmol), (*R*)-1-methoxy-butan-2-ol [Coke, J. L.; Shue, R. S. (1973) J. Org. Chem. 38, 2210-2211] (3.76 g, 36.25 mmol) and triphenylphosphine (9.5 g, 36.25 mmol) in dry

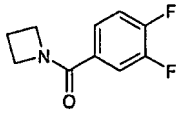
THF (75 mL) which was cooled in an ice-bath. The reaction mixture was allowed to warm slowly to 10°C and stirred for 16 hours. The THF was evaporated, then the residue was dissolved in 30% ethyl acetate in isohexane and cooled in ice. The resultant precipitate was removed by filtration and washed with 10% ethyl acetate in isohexane. The filtrate was evaporated and purified by column chromatography (eluting with 10% ethyl acetate in isohexane) to give the title compound (6.85 g, 68%) as a colourless oil ^{1}H NMR δ ($CDCl_3$): 0.95 (t, 3H), 1.6-1.8 (m, 2H), 3.35 (s, 3H), 3.55 (m, 2H), 3.9 (s, 3H), 4.3 (m, 1H), 5.05 (s, 2H), 6.8 (s, 1H), 7.25 (m, 2H), 7.4 (m, 5H), *m/z* 345 $(M+H)^+$

Intermediate 5: Methyl 3-(benzyloxy)-5-hydroxybenzoate



Potassium carbonate (9 mol) was added to a stirred solution of methyl 3,5-dihydroxybenzoate (5.95 mol) in DMF (6 L) and the suspension stirred at RT under argon. To this was added benzyl bromide (8.42 mol) slowly over 1 hour, with a slight exotherm, and the reaction mixture stirred overnight at ambient temperature. The reaction was quenched cautiously with ammonium chloride solution (5 L) followed by water (35 L). The aqueous suspension was extracted with DCM (1x3 L and 2x5 L). The combined extracts were washed with water (10 L) and dried overnight ($MgSO_4$). The solution was evaporated in *vacuo*, and the crude product purified by column chromatography in 3 batches (flash column, 3x2 kg silica, eluting with an increasing gradient of 10 to 100% DCM in isohexane followed by 50% ethyl acetate in DCM) to eliminate starting material. The crude eluant was purified by HPLC in 175 g batches (Amicon HPLC, 5 kg normal-phase silica, eluting with 20% ethyl acetate in isohexane) to give the title compound (21% yield); ^{1}H NMR δ (d_6-DMSO): 3.8 (s, 3H), 5.1 (s, 2H), 6.65 (m, 1H), 7.0 (m, 1H), 7.05 (m, 1H), 7.3-7.5 (m, 5H), 9.85 (br s, 1H)

Intermediate 6: 1-(3,4-Difluorobenzoyl)azetidine



Oxalyl chloride (1.05 mL, 12.0 mmol) was added to a solution of 3,4-difluorobenzoic acid (1.58 g, 10 mmol) in DCM (50 mL) containing DMF (1 drop). The reaction was stirred at ambient temperature for 16 h then evapourated to dryness. The residue was redissolved in DCM (25 mL) and azetidine hydrochloride (1.12 g, 12.0 mmol) added followed by triethylamine (4.18 mL, 30.0 mmol). The mixture was stirred at ambient temperature for 2 h then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and 1N hydrochloric acid, the organic phase washed with a saturated aqueous solution of sodium bicarbonate followed by brine, dried ($MgSO_4$), and concentrated *in vacuo*. The title compound was crystallized from an ethyl acetate / hexane mixture to give a white crystalline solid (1.0 g, 51%). ^{1}H NMR δ ($CDCl_3$): 2.4 (m, 2H), 4.3 (m, 4H), 7.2 (m, 1H), 7.4 (m, 1H), 7.5 (t, 1H).

Intermediates 7 and **8** were prepared in an analogous fashion to **Intermediate 6**.

Intermediate 7: 3,4-Difluoro-*N,N*-dimethylbenzamide

^{1}H NMR δ ($CDCl_3$): 2.9-3.2 (m, 6H), 7.2 (m, 2H), 7.3 (m, 1H). *m/z* 186 $(M+H)^+$.

Intermediate 8: 1-(3-Chloro-4-fluorobenzoyl)azetidine

^{1}H NMR δ ($CDCl_3$): 2.4 (m, 2H), 4.2-4.4 (m, 4H), 7.2 (m, 1H), 7.55 (m, 1H), 7.7 (m, 1H)

BIOLOGICAL

Tests:

The biological effects of the compounds of formula (I) may be tested in the following way:

(1) Enzymatic activity

Enzymatic activity of recombinant human pancreatic GLK may be measured by incubating GLK, ATP and glucose. The rate of product formation may be determined by coupling the assay to a G-6-P dehydrogenase, NADP/NADPH system and measuring the linear increase with time of optical density at 340nm (Matschinsky et al 1993). Activation of GLK by compounds can be assessed using this assay in the presence or absence of GLKRP as described in Brocklehurst et al (Diabetes 2004, **53**, 535-541).

Production of recombinant GLK and GLKRP:

Human GLK and GLKRP cDNA was obtained by PCR from human pancreatic and hepatic mRNA respectively, using established techniques described in Sambrook J, Fritsch EF & Maniatis T, 1989. PCR primers were designed according to the GLK and GLKRP cDNA sequences shown in Tanizawa et al 1991 and Bonthron, D.T. *et al* 1994 (later corrected in Warner, J.P. 1995).

Cloning in Bluescript II vectors

GLK and GLKRP cDNA was cloned in E. coli using pBluescript II, (Short et al 1998) a recombinant cloning vector system similar to that employed by Yanisch-Perron C *et al* (1985), comprising a colEI-based replicon bearing a polylinker DNA fragment containing multiple unique restriction sites, flanked by bacteriophage T3 and T7 promoter sequences; a filamentous phage origin of replication and an ampicillin drug resistance marker gene.

Transformations

E. Coli transformations were generally carried out by electroporation. 400 mL cultures of strains DH5a or BL21(DE3) were grown in L-broth to an OD 600 of 0.5 and harvested by centrifugation at 2,000g. The cells were washed twice in ice-cold deionised water, resuspended in 1mL 10% glycerol and stored in aliquots at -70^{0}C. Ligation mixes

were desalted using Millipore V series™ membranes (0.0025mm) pore size). 40mL of cells were incubated with 1mL of ligation mix or plasmid DNA on ice for 10 minutes in 0.2cm electroporation cuvettes, and then pulsed using a Gene Pulser™ apparatus (BioRad) at 0.5kVcm^{-1}, 250mF. Transformants were selected on L-agar supplemented with tetracyline at 10mg/mL or ampicillin at 100mg/mL.

Expression

GLK was expressed from the vector pTB375NBSE in E.coli BL21 cells,, producing a recombinant protein containing a 6-His tag immediately adjacent to the N-terminal methionine. Alternatively, another suitable vector is pET21(+)DNA, Novagen, Cat number 697703. The 6-His tag was used to allow purification of the recombinant protein on a column packed with nickel-nitrilotriacetic acid agarose purchased from Qiagen (cat no 30250).

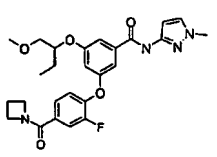
GLKRP was expressed from the vector pFLAG CTC (IBI Kodak) in E.coli BL21 cells, producing a recombinant protein containing a C-terminal FLAG tag. The protein was purified initially by DEAE Sepharose ion exchange followed by utilisation of the FLAG tag for final purification on an M2 anti-FLAG immunoaffinity column purchased from Sigma-Aldrich (cat no. A1205).

(2) Oral Glucose Tolerance Test (OGTT)

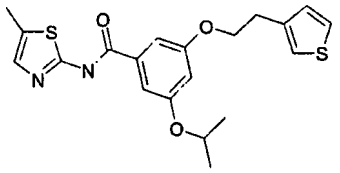
Oral glucose tolerance tests were done on conscious Zucker obese fa/fa rats (age 12-13 weeks or older) fed a high fat diet (45 % kcal fat) for at least two weeks prior to experimentation. The animals were fasted for 2 hours before use for experiments. A test compound or a vehicle was given orally 120 minutes before oral administration of a glucose solution at a dose of 2 g/kg body weight. Blood glucose levels were measured using a Accucheck glucometer from tail bled samples taken at different time points before and after administration of glucose (time course of 60 minutes). A time curve of the blood glucose levels was generated and the area-under-the-curve (AUC) for 120 minutes was calculated (the time of glucose administration being time zero). Percent inhibition was determined using the AUC in the vehicle-control group as zero percent inhibition.

3) Measurements of plasma protein binding of compounds

The plasma protein binding of compounds was measured using the equilibrium dialysis technique (W. Lindner et al, J.Chromatography, 1996, 677, 1-28). Compound was dialysed at a concentration of 20 μM for 18 hours at 37°C with plasma and isotonic phosphate buffer pH 7.4 (1ml of each in the dialysis cell). A Spectrum® 20-cell equilibrium dialyser was used together with Teflon, semi-micro dialysis cells and Spectra/Por®2 membrane discs with a molecular weight cut off 12-14000 Dalton, 47mm (supplied by PerBio Science UK Ltd, Tattenhall, Cheshire). Plasma and buffer samples are removed following dialysis and analysed using HPLCUV/MS (high performance liquid chromatography with UV and mass spec detection) to give the % free level in plasma.



Example 2



Example II107

Compounds of the invention generally have an activating activity for glucokinase with an EC_{50} of less than about 500nM. For example, Example 2 has has an EC_{50} of 0.04 μm.

Example II107 in WO 03/015774 has an EC_{50} of 0.15 μm.

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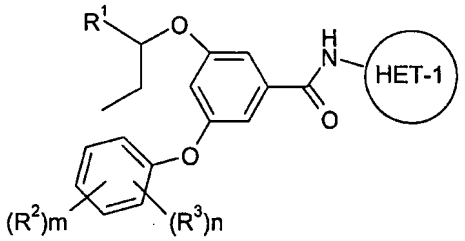
Claims:

1. A compound of Formula (I):



(I)

wherein:

R^1 is methoxymethyl;

R^2 is selected from $-C(O)NR^4R^5$, $-SO_2NR^4R^5$, $-S(O)_pR^4$ and HET-2;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 4-, 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring may optionally be oxidised to a S(O) or $S(O)_2$ group, which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano;

R^4 is selected from hydrogen, (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$], (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and HET-2;

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4;

R^7 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an N-linked, 7 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further heteroatom (in addition to the linking N atom) independently selected from O, S and N, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- group and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an 6-10 membered bicyclic saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further nitrogen atom (in addition to the linking N atom), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-; which ring is optionally substituted on an available carbon or nitrogen atom by 1 substituent selected from hydroxy (not on nitrogen) and R^3;

R^8 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkylamino, di(1-4C)alkylamino, HET-3 (wherein said ring is unsubstituted), (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-4 is a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S;

p is (independently at each occurrence) 0, 1 or 2;

m is 0 or 1;

n is 0, 1 or 2;

provided that when m is 0, then n is 1 or 2;
or a salt, pro-drug or solvate thereof.

2. A compound of the formula (I) as claimed in Claim 1 or a salt, pro-drug or solvate thereof with the proviso that compounds exemplified in WO2004/076420, which would otherwise fall within the scope of this invention, are excluded.

3. A compound of the formula (I) as claimed in Claim 1 or Claim 2 or a salt, pro-drug or solvate thereof wherein R^1 has the (S) configuration.

4. A compound of the formula (I) as claimed in Claim 1, Claim 2, or Claim 3 or a salt, pro-drug or solvate thereof, wherein HET-1 is a 5-membered ring.

5. A compound of the formula (I) as claimed in any one of Claims 1 to 4 or a salt, pro-drug or solvate thereof, wherein R^2 is selected from $-C(O)NR^4R^5$ and $-SO_2NR^4R^5$ and R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclyl ring system as defined by HET-3.

6. A compound of the formula (I) as claimed in any one of Claims 1 to 5, or a salt, pro-drug or solvate thereof, wherein HET-3 is a 4- to 6-membered ring.

7. A compound of the formula (I) as claimed in Claim 4, or a salt, pro-drug or solvate thereof, wherein R^2 is selected from $-C(O)NR^4R^5$ and $-SO_2NR^4R^5$ and R^4 is selected from (1-4C)alkyl [substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$], (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and HET-2.

8. A compound of the formula (I) as claimed in any one of Claims 1 to 4, or a salt, pro-drug or solvate thereof, wherein R^2 is $-SO_2R^4$ and R^4 is selected from (1-4C)alkyl [substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-

6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and -C(O)NR^5R^5], (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and HET-2.

9. A compound of the formula (I) as claimed in any one of Claims 1 to 4, or a salt, pro-drug or solvate thereof, wherein R^2 is HET-2.

10. A compound of formula (I) as claimed in claim 1, which is one or more of the following compounds:
3-fluoro-4-(3-{[(1S)-1-(methoxymethyl)propyl]oxy}-5-{[(1-methyl-1H-pyrazol-3-yl)amino]carbonyl}phenoxy)-N,N-dimethylbenzamide;
3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-{[(1S)-1-(methoxymethyl)propyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide; and
3-[4-(azetidin-1-ylcarbonyl)-2-chlorophenoxy]-5-{[(1S)-1-(methoxymethyl)propyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
or a salt, pro-drug or solvate thereof.

11. A compound of formula (I) as claimed in claim 10, which is one or more of the following compounds:
3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-{[(1S)-1-(methoxymethyl)propyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide; and
3-[4-(azetidin-1-ylcarbonyl)-2-chlorophenoxy]-5-{[(1S)-1-(methoxymethyl)propyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
or a salt, pro-drug or solvate thereof.

12. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 11, or a salt, pro-drug or solvate thereof, together with a pharmaceutically acceptable diluent or carrier.

13. A compound according to any one of Claims 1 to 11 or a pharmaceutically-acceptable salt, solvate or pro-drug thereof for use as a medicament.

14. Use of a compound according to any one of Claims 1 to 11 or a pharmaceutically-acceptable salt, solvate or pro-drug thereof in the preparation of a medicament for treatment of a disease mediated through GLK.

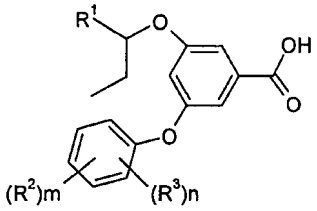
15. Use of a compound according to any one of Claims 1 to 11 or a pharmaceutically-acceptable salt, solvate or pro-drug thereof in the preparation of a medicament for treatment of type 2 diabetes.

16. A method of treating GLK mediated diseases by administering an effective amount of a compound of Formula (I) as claimed in any one of Claims 1 to 11 or salt, solvate or pro-drug thereof, to a mammal in need of such treatment.

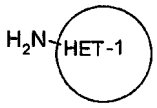
17. The method of Claim 16 wherein the GLK mediated disease is type 2 diabetes.

18. A process for the preparation of a compound of Formula (I) as claimed in any one of Claims 1 to 11, which comprises a process a) to e) (wherein the variables are as defined for compounds of Formula (I) in Claim 1 unless otherwise stated):

(a) reaction of an acid of Formula (III) or activated derivative thereof with a compound of Formula (IV), wherein R^1 is methoxymethyl or a protected version thereof;



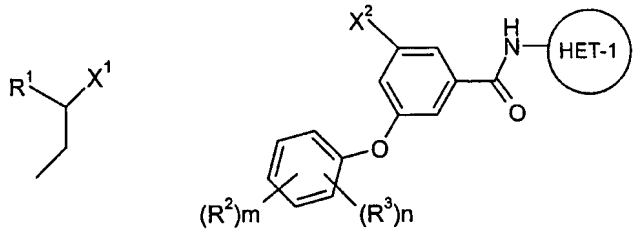
(III)



(IV);

or

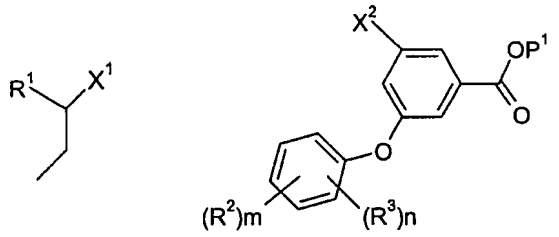
(b) reaction of a compound of Formula (V) with a compound of Formula (VI),



(V) (VI)

wherein X^1 is a leaving group and X^2 is a hydroxyl group or X^1 is a hydroxyl group and X^2 is a leaving group, and wherein R^1 is methoxymethyl or a protected version thereof;

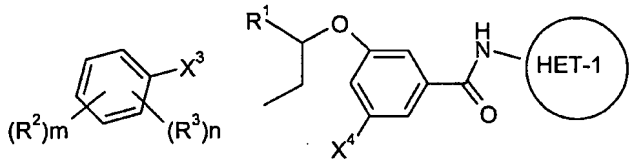
[or by reaction with the intermediate ester Formula (VII), wherein P^1 is a protecting group followed by ester hydrolysis and amide formation];



(V) (VII)

or

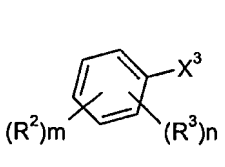
(c) reaction of a compound of Formula (VIII) with a compound of Formula (IX)



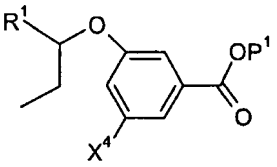
(VIII) (IX)

wherein X^3 is a leaving group or an organometallic reagent and X^4 is a hydroxyl group or X^3 is a hydroxyl group and X^4 is a leaving group or an organometallic reagent, and wherein R^1 is methoxymethyl or a protected version thereof;

[or by reaction or (VIII) with the intermediate ester Formula (X), followed by ester hydrolysis and amide formation];



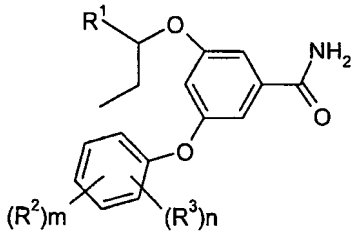
(VIII)



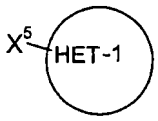
(X)

or

(d) reaction of a compound of Formula (XI) with a compound of Formula (XII),



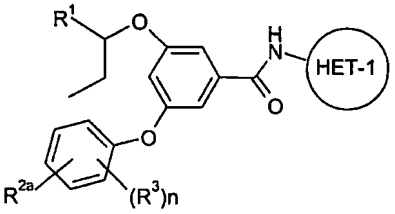
(XI)



(XII);

wherein X^5 is a leaving group, and wherein R^1 is methoxymethyl or a protected version thereof; or

e) reaction of a compound of formula (XIII)



(XIII)

wherein R^{2a} is a precursor to R^2, such as a carboxylic acid, ester or anhydride (for R^2 = $-CONR^4R^5$) or the sulfonic acid equivalents (for R^2 is $-SO^2NR^4R^5$); with an amine of formula $-NR^4R^5$;

and thereafter, if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a salt, pro-drug or solvate.

INTERNATIONAL SEARCH REPORT

Inte al application No
PC[illegible]2005/003888

A. CLASSIFICATION OF SUBJECT MATTER
C07D231/40 C07D213/80 C07D403/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/076420 A (BANYU PHARMACEUTICAL CO., LTD; IINO, TOMOHARU; HASHIMOTO, NORIAKI; NAK) 10 September 2004 (2004-09-10) abstract	1-18
E	-& EP 1 600 442 A (BANYU PHARMACEUTICAL CO., LTD) 30 November 2005 (2005-11-30) page 24; claims 2,4,8,30; examples 9,17,18 page 14, line 45 - line 49 page 12, line 45 page 7, line 2 - page 9, line 48; claims	1-18
	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 January 2006	07/02/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Härtinger, S

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Inter I application No
PC., --2005/003888

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/000267 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; HAYTER, BARRY, RAYMOND; CURRIE) 3 January 2003 (2003-01-03) page 63 - page 64; example R; compound 67 page 80; claims page 25 - page 28	1-18
P,X	WO 2005/080359 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; JOHNSTONE, CRAIG; MCKERRECHER,) 1 September 2005 (2005-09-01) claims; example 18a	1-18
P,X	WO 2005/054200 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; JOHNSTONE, CRAIG; MCKERRECHER,) 16 June 2005 (2005-06-16) claims 1,2,15; examples	1-18
E	WO 2005/121110 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; JOHNSTONE, CRAIG; MCKERRECHER,) 22 December 2005 (2005-12-22) claims; examples	1-18

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INTERNATIONAL SEARCH REPORT

ıational application No.
PCT/GB2005/003888

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 16-17
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 16-17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inter ...nal application No
PC1/GB2005/003888

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 2004076420	A	10-09-2004	AU	2004215514 A1	10-09-2004
			CA	2516407 A1	10-09-2004
			EP	1600442 A1	30-11-2005
EP 1600442	A	30-11-2005	AU	2004215514 A1	10-09-2004
			CA	2516407 A1	10-09-2004
			WO	2004076420 A1	10-09-2004
WO 03000267	A	03-01-2003	BR	0210711 A	20-07-2004
			CA	2451249 A1	03-01-2003
			CN	1520296 A	11-08-2004
			EP	1404335 A1	07-04-2004
			JP	2005500312 T	06-01-2005
			MX	PA03012004 A	26-03-2004
			NZ	530203 A	24-06-2005
			US	2004214868 A1	28-10-2004
			ZA	200309979 A	23-03-2005
WO 2005080359	A	01-09-2005	NONE		
WO 2005054200	A	16-06-2005	NONE		
WO 2005121110	A	22-12-2005	NONE		